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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/232,290	01/15/99	PLUCKTHUN	A MORPHO/7

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EXAMINER	
DECLOUX, A	
ART UNIT	**PAPER NUMBER**
1644	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/232,290	Applicant(s) Pluckthun, A et al.
	Examiner DeCloux, Amy	Group Art Unit 1644

☒ Responsive to communication(s) filed on *Dec 6, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-27* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-27* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☒ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: *EP 96 11 1441.0*.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-27, filed 12-6-99 in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. The priority date of the instant claims is deemed to be the filing date of the parent continuation of International Application PCT/EP97/03792, filed 7-16-97 and published as WO/980262A1 on 1-22-98. Because the foreign priority document EP96 11 1441.0 filed 7-16-96 was not available to the examiner at this time, the examiner could not determine whether the instant claims have priority to said document. If applicant desires priority prior to 7-16-97; applicant is invited to point out and provide documentary support for the priority of the instant claims.

3. Since Applicant desires priority under 35 U.S.C. 119, based upon EP96 11 1441.0, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph.

4. The disclosure is objected to because of the following minor informalities: There appears to be an extra "h" in "algorithm" on page 23, line 18.

5. The specification is objected to because incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference. Therefore, the embedded hyperlinks and/or other forms of browser-executable code disclosed on page 13 and in the legend of Table 1 of the instant specification are impermissible and require deletion.

6. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claims 23-25 lack an antecedent basis for the phrase "association domain".

8 9 10 11 10+12

7. Claims 1-9, 11, and 13-27 are rejected under *35 U.S.C. 112*, first paragraph, because the specification, while being enabling for a DNA sequence comprising a sequence that encodes a modified scFv fragment with mutations in the conserved framework as recited in claim 10 and in claim 12 as it pertains to scFv, does not reasonably provide enablement for any DNA sequence modified to encode and confer increased hydrophiliicity in the interface wherein said sequence encodes a modified

Fab fragment, an Fv fragment, an Fv fragment stabilized by an inter-domain disulphide bond as recited in claims 8, 9 and 11, respectively, or a DNA sequence encoding any modified immunoglobulin superfamily domain or fragment as recited in Claim 1 and its dependent claims with the exception of dependent claim 10 and claim 12 as it pertains to scFv. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, unpredictability in the art, the amount of experimentation required, and the amount of direction or guidance presented.

With the exception of the disclosure of a modified scFv fragment with mutations in the conserved framework , no sequence data regarding a modification conferring increased hydrophilicty of any DNA sequence comprising a sequence that encodes a modified Fab fragment, an Fv fragment, or an Fv fragment stabilized by an inter-domain disulphide bond, as recited in claims 8, 9 and 11, respectively, or a DNA sequence encoding any modified immunoglobulin superfamily domain or fragment, as recited in Claim 1, is found within the specification. There are no DNA sequences provided that encode modifications conferring increased hydrophilicty of any member of the immunoglobulin gene superfamily (with the exception of the disclosure of a modified scFv fragment) which consists of molecules with immunoglobulin-like domains. Members of this superfamily include class I and class II major histocompatibility antigens, immunoglobulins, T-cell receptor alpha, beta, gamma and delta chains, CD1, CD2, CD4, CD8, CD28, the gamma, delta and epsilon chains of CD3, OX-2, Thy-1, the intercellular or neural cell adhesion molecules (I-CAM or N-CAM), lymphocyte function associated antigen-3 (LFA-3), neurocytoplasmic protein (NCP-3), poly-Ig receptor, myelin-associated glycoprotein (MAG), high affinity IgE receptor, the major glycoprotein of peripheral myelin (Po), platelet derived growth factor receptor, colony stimulating factor-1 receptor, macrophage Fc receptor, Fc gamma receptors and carcinoembryonic antigen as taught by Capon et al in U.S. Patent 5,514,582 in Column 1, lines 30-44.

It is not sufficient to define a DNA sequence by its principal biological activity, IE a DNA sequence capable of encoding a modified immunoglobulin superfamily domain with increased hydrophilicity in the interface region, especially in view of the lack of knowledge of the exact identity of which amino acid changes would confer increased hydrophilicity and still function otherwise likewise to its parent molecule as evidenced by Nieba et al (1997) in Protein Engineering 10(4):435-444, (see entire article, especially page 435, column 2, second from the last paragraph) where it is taught that there is limited understanding of how specific sequence modifications in those parts of the antibody molecule which are not directly involved in antigen recognition can change the properties of recombinant Fv and scFv. Accordingly this same paucity of understanding can be applied to the unknown effect on the molecule's original

properties upon modification of domains of members of any immunoglobulin superfamily, including an Fab fragment, an Fv fragment and an Fv fragment stabilized by an interdomain di-sulphide bond as encompassed in the instant claims. Due to the different secondary structure of an Fab fragment, an Fv fragment and an Fv fragment stabilized by an interdomain di-sulphide bond compared to that of a scFv fragment, modifications in certain residues of an scFv fragments as disclosed in the instant specification might not have the same effect as identical modifications in an Fab fragment, an Fv fragment and an Fv fragment stabilized by an interdomain di-sulphide bond because the problem of predicting functional aspects of the product from mere sequence data and what changes can be tolerated is complex and well outside the realm of routine experimentation. *In re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Without such guidance, the DNA sequences encoding for modifications conferring increased hydrophilicity in an interface region in an immunoglobulin superfamily domain fragments and still maintain the properties that define the molecule as an immunoglobulin superfamily member is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue. See *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). Therefore, there is no evidence of record to show that one skilled in the art would be able to practice the invention as claimed without an undue amount of experimentation.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention and this is not sanctioned by the statute.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

9. Claims 1-27 are rejected under *35 U.S.C. § 112*, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

A) Claims 23-25 are indefinite in the recitation of the phrase "association domain" because it is not clear what said phrase means and there is insufficient guidance for interpreting said phrase in the instant specification.

B) Claim 1, line 3, and its dependent claims are indefinite in the recitation of "wherein said modified IGSF differs" because it is not clear how a family can differ from

a domain or fragment. Perhaps the applicant meant to insert "fragment or domain" between "IGSF" and "differs".

C) Claim 5 is indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of ..." with the use of the conjunction "and" in listing the species. See MPEP 2173.05(h).

10. The following is a quotation of the appropriate paragraphs of *35 U.S.C. § 102* that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> Or
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-2, 5-7, 10, 12-13, 18-22 and 26-27 are rejected under 35 U.S.C. 102(a) as being anticipated by Neiba et al (Protein engineering 10(4):435-444, April, 1997).

Neiba et al teach a DNA sequence encoding a scFv fragment of the antibody 4-4-20 (a member of the immunoglobulin superfamily (IgSF)) that was modified by site-directed mutagenesis to encode a product in which hydrophobic patches in its former interface have been replaced negative charges (see entire article, especially page 444, last paragraph, and page 436, last two paragraphs of column 1).

With regard to claim 2, Neiba et al teach replacing residue 84 with hydrophilic residues and that residue 84 is in a hydrophobic surface involving the V/L interface residues (see page 442, column 2, last paragraph). With regard to Claim 5, Neiba et al teach mutations encoding the following amino acid substitutions; E, N and D (see Table II and the Materials and Methods section on page 436). With regard to claims 6 - 7 and 10, Neiba et al teach the IgSF domain is part of an antibody scFv fragment (page 436, last two paragraphs of column 1). With regard to claim 12, Neiba et al teach mutations in the interface region that comprises residues 15 for VL and residues 11 and 88 for VH (see Table II). With regard to Claims 13 and 18-22, Neiba et al teach the DNA sequence encoding the above described mutations which also encodes an additional moiety of the FLAG tag and the HIS5 tag which can bind nickel (see Materials and Methods section on page 436, column 1). With regard to claims 26 and 27, Neiba et al teach a vector comprising a DNA sequence encoding a scFv fragment of the antibody 4-4-20 (a member of the immunoglobulin superfamily (IgSF)) that was modified by site-directed mutagenesis to encode a product in which hydrophobic patches in its former interface have been replaced negative charges (see

entire article, especially Materials and Methods section on page 436, column 1, and page 444, last paragraph).

Therefore, the reference teachings anticipate the claimed invention.

Applicant cannot rely upon the foreign priority paper EP96 11 1441.0, filed 7-16-96 to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

12. Claims 1-7, 10, 13-17, and 26-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnson et al (WO 92/01787)(IDS).

Johnson et al teach an analogue of a single chain variable domain of a member of an immunoglobulin or immunoglobulin superfamily, in which said analogue one or more interface amino acid residues of the domain is altered ,wherein the said altered amino acid is substituted with a residue so that the analog is more hydrophilic than the unaltered domain, (see entire article, especially pages 6 and 7, last and first paragraph, respectively) and teaches that said analogues are obtained using site directed mutagenesis and a recombinant expression system, (see entire article, especially pages 9-10) as recited in Claims 1 and 26-27. Johnson et al teach that said analogues comprising domains which are synthetic analogs of a natural single variable domain of a member of an immunoglobulin superfamily (see entire article, especially page 1, lines 6-9) such as single chain variable domains (see entire article, especially page 19). With regard to claims 2-7 and 10, Johnson et al teach that said alteration of a single chain variable domain of a member of an immunoglobulin or immunoglobulin superfamily may be by way of amino acid substitution, deletion, addition inversion, (see entire article, especially page 7, lines 12-15) and the amino acids substituted include Q, T E D S G or N (see entire article, especially pages 7 and 8). With regard to claims 13-14, Johnson et al teach said single chain moieties may be further coupled an additional moiety that can be enzymic, florescent, radiolabeled or a portion of an immunoglobulin (see entire article, especially page 8, lines 17-21). With regard to claims 15-17, Johnson et al also teaches cloning the recombinant products into fd phage (see entire article, especially page 20 , line 1) and also that said analog or derivative can be displayed on a phage as a fusion with gene III protein of filamentous bacteriophage (see entire article, especially page 20 , lines 15-23).

Therefore, the reference teachings anticipate the claimed invention.

13. The following is a quotation of *35 U.S.C. § 103* which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under *subsection (f) or (g)* of *section 102* of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-7, 10, 13-17, 18-22, and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson et al (WO 92/01787)(IDS) in view of Jenkins et al (PNAS 92:6057-6061, 1995)(IDS) and Knappik et al (Biotechniques 17(4):754-761, 1994)

Johnson et al teaches as above, however Johnson does not teach a DNA sequence with an additional moiety capable of binding a metal ion, as recited in claims 18-19, or a peptide or labeling tag moiety as recited in claims 20-22.

Jensen et al teaches DNA recombinant methods of producing mutants of the HIV integrase gene by replacing hydrophobic residues to increase its solubility (see page 6060, column 2, third paragraph of Discussion section). Jensen et al also teaches that the recombinant methods include the use of a histidine tag that allows rapid purification of the expressed protein on a nickel chelating column (see entire article, especially page 6057, column 2, last paragraph).

Knappik et al teaches that the FLAG peptide has been successfully used as a detection and purification tag of antibody fragments expressed in E. Coli (see entire article, especially page 761, column 1, first sentence).

Therefore, it would have been obvious to one of skill in the art at the time the invention was made to have made and used a DNA sequence as recited in Claims 1-7, 10, 13-17, and 26-27 in view of the teachings of Johnson et al. for the reasons stated in the above 102b rejection in Section 14 of this office action.

With regard to claims 18-22, it would have been obvious to one of skill in the art at the time the invention was made to have made and used a DNA sequence as taught by Jonson et al that had an additional moiety of a histidine tag as taught by Jensen et al, or an additional moiety of a FLAG peptide as taught by Knappik et al because both Jensen et al and Knappik et al teach that said moieties aid in the detection and purification of expressed proteins, especially antibody fragments, and one would expect that it would also aid in the detection of recombinant mutants of said antibody fragments.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy DeCloux whose telephone number is (703) 306-5821. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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May 8, 2000

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